SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4-aminophenol

EC No 204-616-2

CAS No 123-30-8

Evaluating Member State: Italy

Dated: 5 July 2021

Evaluating Member State Competent Authority

MSCA Italy National Institute of Health on behalf of Ministry of Health
Viale Regina Elena, 299 - 00161 Rome, Italy in cooperation with Italian National Institute for Environmental Protection and Research (ISPRA). Via Brancati, 48 - 00144 Rome, Italy

Tel.: +390649902061
FAX: +390649902286
Email: leonello.attias@iss.it

Year of evaluation in CoRAP: 2020

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, 4-aminophenol, was originally selected for substance evaluation in order to clarify concerns about:

- Mutagenicity
- Skin sensitisation
- Other hazard based concern: STOT RE

No additional concerns were identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A compliance check was initiated by ECHA during drafting of this document, in relation to the concerns above.

4-aminophenol is covered by the Seveso III Directive (Directive 2012/18/EU in the Seveso category E1).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

On the basis of the available information, an harmonised classification of the substance is envisaged by evaluating MSCA (eMSCA), as a follow-up at EU level with the following hazard categories: Skin Sens. 1A, H317 (May cause an allergic skin reaction) and STOT RE 1, H372 (Causes damage to organs through prolonged or repeated exposure).

Moreover, in case of a positive result in the new *in vivo* germ cells study requested under compliance check (CCH) by ECHA, an update of the Harmonised Classification and Labelling should be performed.

Due to its structural similarity to other aminophenols, 4-aminophenol (EC number 204-616-2) was originally selected to be jointly evaluated during the substance evaluation process with bis(4-hydroxy-N-methylanilinium) sulphate (EC number 200-237-1), 3-aminophenol (EC number 209-711-2) and 5-amino-o-cresol (EC number 220-618-6).

Even if the evaluation process was performed separately for the above mentioned substances, the follow-up for 4-aminophenol could be used to classify other members of the group.

In case of classification of 4-aminophenol as mutaten category 1B, a RMOA could be performed in order to clarify all potential concerns.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

A harmonized classification of the substance is envisaged as a follow-up at EU level for indicated human health.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Annex XV dossier for harmonised Classification	tbd	Competent Authority of Italy
RMOA	Depending on review of harmonised classification	Competent Authority of Italy

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

4-aminophenol was originally selected for substance evaluation in order to clarify concerns about:

- Mutagenicity
- Skin sensitisation
- Other hazard based concern: STOT RE

No additional concerns were identified.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Mutagenicity	The evaluation performed during the SEV process highlighted a data gap on germ cells that should be addressed through CCH.
Skin sensitisation	The available data was considered sufficient to conclude that the substance is a strong skin sensitiser. C&L process is to be initiated for sub-categorisation 4-aminophenol as Skin Sens 1A - H317.
STOT RE	The available data was considered sufficient to conclude that the substance shows effects on kidney after repeated exposure. C&L process is to be initiated to classify 4-aminophenol as STOT RE 1 - H372.

7.2. Procedure

Pursuant to Article 44(2) of REACH, 4-aminophenol was included on the Community rolling action plan (CoRAP) for evaluation in 2020. The Competent Authority of Italy was appointed to carry out the evaluation. The substance evaluation started on 18 March 2020.

Due to structural similarity, the substances, bis(4-hydroxy-N-methylanilinium) sulphate (EC number 200-237-1), 4-aminophenol (EC number 204-616-2), 3-aminophenol (EC number 209-711-2) and 5-amino-o-cresol (EC number 220-618-6) were originally selected to be jointly evaluated during the substance evaluation process.
These substances belong to the aminophenol's chemical class, differing in the relative position of amino and hydroxyl groups on the aromatic ring and in the presence/absence of a methyl substituent (either on the ring or on the amino group).
Aminophenols are potentially reactive chemicals via metabolic pathways involving the formation of electrophilic and/or quinone imines intermediates. The initial evidence induced the eMSCA to perform an evaluation of the substances on human health. eMSCA has decided to evaluate the four substances separately.

The substance evaluation was targeted to clarify concerns on mutagenicity, skin sensitisation and specific target organ toxicity. Other endpoints were not evaluated.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	4-aminophenol
EC number:	204-616-2
CAS number:	123-30-8
Index number in Annex VI of the CLP Regulation:	612-128-00-X
Molecular formula:	C6H7NO
Molecular weight range:	
Synonyms:	1-hydroxy-4-aminobenzene, p-aminophenol

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid
Vapour pressure	0.005 Pa at 25 °C
Water solubility	6 500 mg/L at 25 °C
Partition coefficient n-octanol/water (Log Kow)	-0.09 at 25 °C
Flammability	The substance is non-flammable based on the experimental result.
Explosive properties	Based on structure and oxygen balance the material is not explosive and testing was waived based on it being scientifically unjustified.
Oxidising properties	The substance contains no oxidising groups and all (oxygen, halogen) atoms are bonded directly to carbon and hydrogen.
Granulometry	The amount of fine dust (particle size fraction < 32 µm) was 2.49 % and mass fraction > 125 microns was 86.27%.

Stability in organic solvents and identity of relevant degradation products	--
Dissociation constant	5.48 T 20 °C

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☒ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

This substance is used by consumers, by professional workers (widespread uses), in formulation or re-packing and at industrial sites.

Table 7

USES	Use(s)
Uses as intermediate	See below.
Formulation	This substance is used in the following products: cosmetics and personal care products.
Uses at industrial sites	This substance has an industrial use resulting in manufacture of another substance (use of intermediates). This substance is used for the manufacture of chemicals.
Uses by professional workers	This substance is used in cosmetics and personal care products and leather treatment products. This substance is used in formulation of mixtures and/or re-packaging. This substance is used for the manufacture of chemicals and textile, leather or fur.
Consumer Uses	This substance is used in cosmetics and personal care products.
Article service life	---

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

The substance is currently listed on Annex VI of CLP Regulation ((EC) No 1272/2008).

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
612-128-00-X	4-aminophenol	204-616-2	123-30-8	Acute Tox. 4 * Acute Tox. 4 * Muta. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H332 H341 H400 H410	H302 H332 H341 H410	

7.6.2. Self-classification

- In the registration(s):

Acute Tox. 4 H302
Acute Tox. 4 H332
Skin sens. 1 H317
STOT RE 2 H373 (Affected organ kidney)

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Not evaluated.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Sensitisation

7.9.3.1 Skin sensitisation

The evaluation of the skin sensitisation potential of 4-aminophenol is based on both animal and human studies.

Animal studies

Two animal studies are available in the registration dossier and in the CSR on 4-aminophenol.

The first skin sensitisation study (non-LLNA) was an experimental study conducted on guinea pig (Kleniewska, D. and Maibach, H., 1980). Even if the details reported are limited, it is acceptable for assessment as the test procedures were based on scientific principles and standards following a protocol equivalent or similar to OECD TG 406 (Buehler test). The induction exposure (epicutaneous, occlusive) was made at 2% by four 24hr occlusive patches on alternate days. The challenge exposure (epicutaneous, occlusive) was made after the induction at 0.1, 0.5, 1.0, 2% of 4-aminophenol. The results at 48 h after the challenge were the following: 3 out of 10 were positive at dose 0.1% (30% of sensitised animals), 5 out of 10 at dose 0.5% (50% of sensitised animals), 6 out of 10 at dose of 1% (60% of sensitised animals) and 9 out of 10 at dose of 2%.
The Registrant(s) conclusion on this study is that 4-aminophenol was a skin sensitiser in the guinea pig. The eMSCA agrees with the Registrant(s) conclusion.

The second skin sensitisation was a Freund's complete adjuvant test equivalent or similar to OECD TG 406 conducted on guinea pigs using two methods of induction (Dossou, K.G. et al., 1985). For the first method, Freund's Adjuvant was injected into the foot pad of the hind paw and 0.18 mmol/L (corresponding to 0,0019%) the test item was administered topically twice (over two days). For the second method, a preparation containing a 1:1 ratio of Freund's Adjuvant and 0.18 mmol/L (corresponding to 0,0019%) test item (in distilled water) was injected into the foot pad of the hind paw.
After a 16-day waiting period, both groups of animals were challenged with a dose of 0.09 mmol/L (corresponding to 0,00098%) in the lumbar region.
Animals tested under the first method of induction exhibited no sensitization reactions, while 40% of those tested under the second method of induction were positive for sensitization.
The Registrant(s) conclusion on this study is that 4-aminophenol was a skin sensitiser when the induction with Freund's adjuvant was used followed by challenge 16-days later. The eMSCA agrees with the Registrant(s) conclusion.

Human information

The key information based on human experience includes the following studies as presented by the Registrant(s) in the CSR. The same studies has been evalutated by the SCCS (SCCS, 2011)

- Among 60 patients from a dermatology clinic who were tested with 1% *p*-aminophenol, 7 (12%) were positive.
- Between 1973 and 1977, 4600 patients were tested for sensitization to benzidine. Of the 5.0% who were positive, 16.4% also had positive reactions to para-amino compounds. 1% of the patients (n=46) had a positive reaction to *p*-aminophenol.
- Between 1974 and 1984, 32 professional hairdressers with hand dermatitis due to use of hair dyes were patch tested for sensitization to these products. Twenty-two subjects had a positive reaction to hair dyes and 25% of these were positive when tested with *p*-aminophenol.
- 408 patients with eczema were patch tested for reactions against *p*-aminophenol. In response to the application of 1% *p*-aminophenol in Vaseline, 3% of the patients were positive.
- Of 13 female cosmetologists with hand, face, and/or axiliary dermatitis, 4 were patch tested with a concentration of 1% *p*-aminophenol in Vaseline using standards approved by the International Contact Dermatitis Research Group. Of these, one person tested positive for sensitization with *p*-aminophenol.
- Two groups of hairdressers were tested for sensitization to *p*-phenylenediamine (PPD).
- 32 were negative for sensitization and 7 were positive. When the same subjects were tested for sensitization to *p*-aminophenol, the 32 who were negative with PPD were also negative with *p*-aminophenol. One of the 7 who was positive with PPD was also positive with *p*-aminophenol.

The conclusion of the SCCS is that *p*-aminophenol is a strong sensitizer.
The eMSCA agrees with the SCCS conclusion.

eMSCA conclusion on skin sensitisation

The available information in the CSR suggests that based on both two animal studies and human evidence *p*-aminophenol is a strong skin sensitiser and the available data warrants the classification as Skin Sensitiser 1A, H317.

7.9.4. Repeated dose toxicity

Repeated dose toxicity: oral

Three oral studies with 4-aminophenol are presented both in the CSR and in the Registration dossier.
In a first subchronic study, males and females of Sprague-Dawley rat were treated by gavage for 90 days (13 weeks) according to OECD TG 408 (unpublished report 1995). The doses were 0, 10, 30 and 100 mg/kg bw/day.
At 30 or 100 mg/kg bw/day was recorded alteration of the epithelium of the renal tubules associated in almost all animals from weak to marked tubular basophilia which is one of the most common manifestations of damage induced to the nephron. This could be followed by degeneration or it can represent excessive cellular turnover.
At the dose of 10 mg/kg/day, there was only a slightly lower body weight gain in females only, and this dose was considered to be at or close to a NOEL.
In this study a NOAEL of 10 mg/kg bw/day is derived by the Registrant(s) as the effects on kidney were observed at 30 mg/kg bw/day which is to be considered the LOAEL.
eMSCA agrees with the Registrant(s) conclusion.

In a second study males and females of Sprague-Dawley rat were treated by gavage for 28 days according to OECD TG 407 (unpublished report 1998). The doses were 0, 4, 20, 100 and 500 mg/kg bw/day.
The urinalysis data showed dark brown urine in both sexes and an increase in urine epithelial cells and kidney weight gain in females only at 100 mg/kg bw/day.
Histopathological analysis highlights basophilic tubules in both males and females at 100 mg/kg bw/day.
A NOAEL of 20 mg/kg bw/day was indicated by the Registrant(s).
eMSCA agrees with the Registrant(s) conclusion.

In a third study males and females of Sprague-Dawley rats was dosed orally (feed) for 13-week with *p*-aminophenol. The study (C.M. Burnett et al, 1989) is poorly reported: However this study highlights the effects on kidney (at histopathological examination), indicated as a slight increase in nephrosis at 133 mg/kg bw/day confirming the hazard on kidney of *p*-aminophenol founded in the other studies reported both in the CRS and in the registration dossier. For this study Registrant(s) identifies 133 mg/kg/bw as LOAEL. As a conseguence the NOAEL of this study is therefore 47 mg/kg bw/day. The eMSCA agrees with the Registrant(s)' conclusion.

eMSCA conclusion on repeated dose toxicity

Therefore, as a reliable subchronic study toxicity study (90 days - 13 weeks) is available showing toxicity effects on kidney, for which the observed NOAEL is 10 mg/kg bw/day, the eMCSA proposes that a CLH proposal is warranted to classify *p*-aminophenol as STOT RE 1; H372.

7.9.5. Mutagenicity

Genotoxicity *in vitro* studies
The results of an unpublished report with an OECD TG 471 assay is available in the CSR (unpublished report, 1998). The test was performed on *Salmonella thyphimurium* TA 1535, TA 1537, TA 98 and TA 100 strains and *Escherichia coli* WP2 uvr A. The test was conducted with the following conditions: without S9 mix; 0-2000 µg/plate in TA100, TA1535 and TA1537; 0- 5000 µg/plate in TA98; 0- 5000 µg/plate in WP2 uvrA; with S9

mix at 0-5000 µg/plate in TA100, TA1535 and TA1537; 0-5000 µg/plate in TA98 and WP2 uvrA.
The Substance, 4-Aminophenol, did not induce mutations in the *S. typhimurium and E. coli* strains in these test conditions.
These results were also confirmed in a publicly available dossier (Zeiger E., 1988).

Moreover, the negative results in TA 1535, TA1537, TA 98 and TA 100 are confirmed in another study (Zeiger E., 1988) available in literature. For *Escherichia coli* WP2*uvr*A/pKM101 an available literature study (Unpublished report, 1998) reported positive results without S9 mix.

An unpublished report with an OECD TG 473 assay is reported in the CSR. The test was performed to analyse chromosomal aberration (CA) in human lymphocytes *in vitro* after 4-aminophenol administration (Unpublished report 1990).
In the test 1, lymphocytes were treated with 13.0, 19.0, 25.0 µg/ml of test substance without S9 mix for 48 h after the initiation of cultures and 20 h continuous treatment; and with 960.4, 1372, 1960 µg/ml of the test substance with S9 mix for 48 h after the initiation of cultures treatment (17 h harvest). The top dose for analysis was one at which a 50-80% reduction in mitotic index occurred. Numbers of aberrant cells in all cultures treated with 4-aminophenol were significantly higher than those observed in concurrent solvent controls, with cultures in the absence and presence of S9 mix exhibiting 53% to 85% and 28% to 63% aberrant cells, respectively. Historical control ranges were exceeded in all treated groups both in the absence and presence of S9 mix. The increases in the proportions of aberrant cells was mainly attributable to deletion-type aberrations. Under the experimental conditions, 4-aminophenol was genotoxic (clastogenic) in human lymphocytes *in vitro*.
An unpublished report with an OECD TG 473 assay (CA in mammalian cells) performed in cultured Chinese hamster lung (CHL/IU) cells is also reported in the CSR (Unpublished report, 1998). CHL/IU cells were treated with 0, 0.0025, 0.0050, 0.010 mg/mL of 4-aminophenol without S9 mix (24h continuous exposure and 48h continuous exposure); at higher doses (0, 0.013, 0.025 mg/mL) –S9 mix in a short term exposure (6 hours); the effect of S9 mix was tested only in a short-term exposure at higher doses (0, 0.28, 0.55, 1.1 mg/mL). Structural chromosomal aberrations were induced at 0.0025, 0.0050 and 0.010 mg/ml (all concentrations) with continuous treatment, and at 0.013 and 0.025 mg/ml (low and high concentrations) with short-term treatment, without an exogenous metabolic activation system. No CA were observed in presence of S9 mix in a short treatment exposure. Polyploidy was not induced in any treatment group.

No *in vitro* gene mutation data in mammalian cells are reported in the CSR but this information is reported in the opinion 1409 of the *Scientific Committee on Consumer Safety* (SCCS) published in 2011. Briefly, a gene mutation in CHO - K_1-BH_4 cells (*HPRT* locus) was performed after 4-Aminophenol treatment in the 1990 (Oberly T.J. et al., 1990). In this assay a biologically relevant increase in mutant frequency compared to concurrent controls was not observed, either in the absence or in the presence of S9-mix, but this test is considered inadequate due to weekness of the test and also because it was not conducted in compliance with OECD TG. A gene mutation in mouse lymphoma cells (TK locus) is also available (Majeska, J. B. et al., 1995). Cells were treated for 4 hr in the absence of S9 mix and assayed for gene mutation at *TK* locus. Under the experimental conditions used, *p*-aminophenol was genotoxic in this mouse lymphoma assay at the *tk* locus. Since at higher concentrations smaller colonies dominate, the results point to a clastogenic effect. The test was not conducted in compliance to OECD TG. In the same assay 4-aminophenol was tested in CHO-K1-BH4 cells (HGPRT locus) (Majeska, J. B. et al., 1995). In CHO cells, there was no increase in thioguanine-resistant cells at dose levels that reduced cell survival to < 20%. The results observed in CHO and Mouse lymphoma cells confirm the ability of 4-aminophenol to induce only clastogenicity in cultured cell lines, revealed as small colonies in mouse lymphoma gene mutation assay (TK locus).

Genotoxicity *in vivo* studies

The following three *in vivo* unpublished micronucleus assay with 4-aminophenol are reported in the CSR:

- an *in vivo* micronucleus assay performed according to OECD Guideline 474 in CD-1 mice by gavage at 0, 125, 250, 500 mg/kg bw (Unpublished report, 2007). The frequency of micronucleated polychromatic erythrocytes was significantly increased in males at a dose of 125 mg/kg and above. After 24h of administration, an inhibition of bone marrow cell proliferation (measured as PCE/NCE ratio) was observed at a dose of 125 mg/kg and above under the test conditions. 4-aminophenol is clastogenic and/or aneugenic in this mouse bone marrow micronucleus test.
- an *in vivo* micronucleus assay performed according to OECD TG 474 in Swiss male and female mice by single gavage at 0, 170, 250, 500 mg/kg bw (Unpublished report, 1992). At 24 hours the PCEs/NCEs ratio was not significantly altered after treatment as compared with controls; this may reflect the lack of cytotoxicity of the test agent at 24 hours sacrifice time. At 24 hours, a statistically significant and biologically relevant increase in the incidence of micronucleated polychromatic erythrocytes over the concurrent vehicle control values were observed for all dose levels. At 48 hours, a statistically significant and biologically relevant increase in the incidence of micronucleated polychromatic erythrocytes over the concurrent vehicle control values was observed. 4-aminophenol induces statistically significant increase in the frequency of micronucleated PCEs. Therefore, it is considered clastogenic and/or aneugenic in this mouse bone marrow micronucleus test.
- an *in vivo* micronucleus assay performed accordingly to OECD TG 474 in Sprague-Dawley male and female rats by gavage at 0, 12, 30 mg/kg bw for 13 weeks was performed (Unpublished report, 1995). The PCEs/NCEs ratio was not significantly altered after 13 weeks treatment as compared to controls. No statistically significant and biologically relevant increase in the incidence of micronucleated polychromatic erythrocytes over the concurrent vehicle control values were observed in both sexes given 12 or 30 mg/kg bw. Under the conditions of the test it can be concluded that 4-aminophenol at doses at which no signs of clinical toxicity were recorded, does not induce a statistically significant increase in the frequency of micronucleated PCEs.

The Substance 4-aminophenol was also tested for *in vivo* chromosomal aberration (CA) in an unpublished OECD TG 475 assay, reported in the CSR (Unpublished report, 2000). The assay was performed in male and female Wistar rat at 200, 400 and 800 mg/kg bw. Dose levels were determined by a preliminary dose range finding study. Sacrifice was performed 24 h (all groups) or 48 h (top dose group) after substance administration. A total of at least 100 metaphases were examined from each animal; only cells with a modal number of chromosomes (n = 42$\pm$ 2) have been taken into account. Mitotic Index was determined on 1000 cells. Statistically significant increase in the number of CA was observed only at the top dose but a dose-response trend was observed even at lower doses. The author of the study, considered the statistically significant increase observed at 800 mg/kg at 24 h harvest time as devoid of biological significance due to the fact that the total frequency of aberrant metaphases is similar to that seen in general. The low baseline frequency (0.1%) may be the reason for the statistical significance observed. In our view the data should be considered as a supportive evidence of the clastogenicity effects reported in the previous *in vivo* MN assays.

The Substance 4-aminophenol was also tested for DNA repair/damage ability in an UDS assay (OECD TG 486) performed in male Wistar rats treated orally by gavage at 285 and 1425 mg/kg bw (Unpublished report, 1990). The top dose was approximately 80% of the LD50 and a lower dose 285 mg/kg bw, the 0.2 times this top dose was also selected. Slides were examined microscopically after development of the emulsion and staining, and the Ner Grains (NG) was determined for each slide, animal and dose group. Negative (solvent) control animals gave a mean NG value of less than 0. NG values were increased by N-2-Fluorenylacetamide (2-AAF) and N-Nitrosodimethylamine treatment to more than +10. Treatment with 285 mg/kg or 1425 mg/kg of 4-aminophenol did not produce a mean NG value greater than -2.2, nor were more than 5.2% of the cells found to be in repair. Both negative and positive controls were within historical responses and it can be concluded that

4-aminophenol has no genotoxic activity in this test under the experimental conditions employed.

An old dominant lethal assay (performed before the OECD 478 publication) in Sprague-Dawley rats is also available in literature (Burnett T.M. et al, 1989) and reported in the CSR. 4-Aminophenol was fed in the diet to groups of 20 male Sprague-Dawley rats at levels of 0.07, 0.2 or 0.7% for up to 20 weeks. After 20 weeks, the 20 males/group selected for the dominant lethal study were housed individually with two untreated virgin females obtained from the same supplier. Cohabitation continued until mating occurred for up to 6 days, after which the procedure was repeated with two new females/male. In the first mating, in the high-dose group there was a statistically significant increase in the total number of resorptions (due largely to one litter all resorbed) but not litters with resorptions. However, no such increase was observed in the second mating. In order to clarify these findings, the study was repeated in an identical fashion but with a short exposure (8-weeks feeding period). The combined data for the two matings in this second study revealed no increases in the numbers of non-viable foetuses.

In **conclusion**, the *in vitro* experimental data showed a clear genotoxic effect (clastogenic and/or aneugenic) of 4-aminophenol (positive CA in human lymphocytes + and – S9; positive in CHL/IU cells –S9 and negative –S9 in a short term exposure) while its ability to induce gene mutation is unlikely (negative results in AMES). The positive result observed in gene mutation of mouse lymphoma L5178Y cells could be the effects of clastogenic activity of 4–aminophenol, in fact mutant colonies were distributed over a wide range of sizes but with increasing concentrations, the smaller colonies were predominant. The clastogenic effect observed *in vitro* is also confirmed in the *in vivo* micronucleus studies in CD1 mice or in Swiss mice. The negative results reported in MN in rats are probably due to a very low dosage. Supporting evidence of the clastogenicity are also reported in the CA assay in rats by gavage. Based on these data a classification as mutagen category 2 is supported, but the information on germ cells are not sufficient to draw a conclusion on the hazard. Only an old dominant letal study is available and no information from ADME studies can be derived about the ability of 4-aminophenol to reach gonads.

The available and current information is not sufficient to draw a firm conclusion on the mutagenicity of 4-aminophenol, further information is needed on germ cells. The eMSCA has advised ECHA to request a new *in vivo* test through CCH.

7.9.6. Carcinogenicity

Not evaluated.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not evaluated.

7.9.8. Hazard assessment of physico-chemical properties

None impacting human health.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA has focused the evaluation on the derivation of DNELs for long-term systemic effects following dermal/inhalation exposure for workers.

eMSCA agrees with the Registrant(s) regarding the derivation of the dermal DNEL while disagrees for the inhalation one, because, the Registrant(s) did not take into account the differences in the respiratory volume between the general population and workers.

Thus, eMSCA recalculated an inhalation DNEL of 0.35 mg/m³ instead of the value of 52.5 mg/m³ reported by the Registrant(s) in the CSR, applying the correct formula (reported in the Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose [concentration] -response for human health, Example B. 3 page 62 of the guidance).

The Registrant(s) is recommend to update both the CSR and the IUCLID dossier taking into account the value reported below. Consumer risk assessment is within the scope of Regulation (EC) No 1223/2009 (see section 7.12.1.2).

Table 9

CRITICAL DNELS/DMELS				
Endpoint of concern	**Type of effect**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Dermal Workers repeated dose toxicity	Long-term - systemic effects	NOAEL: 100 mg/kg bw/day	DNEL: 1 mg/kg bw/day based on AF of 100)	**AF** for interspecies differences: 10 **AF** for intraspecies differences: 5 **AF** for differences in duration of exposure: 2 **AF** for uncertainty in route-to-route extrapolation: 1 **AF** for dose-response relationship: 1 **AF** Other aspects relating to the dataset: 1 **Overall Assessment Factor**: 100
Inhalation Workers repeated dose toxicity	Long-term - systemic effects	NOAEC: 8.81 mg/m³ (starting from a NOAEL oral of 10 mg/kg bw/d)	DNEL: 0.35 mg/m³ (based on AF of 25)	**AF** for interspecies differences: 2.5 **AF** for intraspecies differences: 5 **AF** for differences in duration of exposure: 2 **AF** for uncertainty in route-to-route extrapolation: 1 **AF** for dose-response relationship: 1 **AF** Other aspects relating to the dataset: 1 **Overall Assessment Factor**: 25

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

On the basis of the available information, an harmonised classification of the substance is envisaged by eMSCA, as a follow-up at EU level with the following hazard category: Skin Sens. 1A, H317 (May cause an allergic skin reaction) and STOT RE 1, H372 (Causes damage to organs through prolonged or repeated exposure).

The available data cannot support a firm conclusion about the mutagenicity, therefore a new study to address the genotoxicity to germ cells, should be required by ECHA through CCH.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Three exposure scenarios (ES) are presented by the Registrant(s) in the CSR for this substance:

- The first is for the manufacturing of the substance which includes 5 contributing ES for workers and one exposure scenario for environmental release.
- The second is for industrial use of the substance resulting in the manufacture of another substance (use as intermediate) with 2 contributing exposure scenarios.
- The third is describing the incidental presence of the substance in a mixture for use as a fertilizer on agricultural land with professional users applying this to the soil.

The eMSCA considers that the worker exposure assessment provided by the Registrant(s) is acceptable.

7.12.1.2. Consumer

The only direct exposure of the general population to 4-aminophenol is via its use in commercial cosmetics and personal care products. Regarding this issue eMSCA highlights that, in accordance with Article 14.(5) (b) of the REACH regulation, the Chemical Safety Report does not need to include consideration of the risks to human health from the end use in cosmetic products within the scope of Regulation (EC) No 1223/2009. However an evalutation of 4-aminophenol in the contest of consumer use, has been made by SCCS in 2011 reporting in the opinion that the use of p-aminophenol with a maximum on-head concentration of 0.9% in oxidative hair dye formulations does not pose a risk to the health of the consumer, apart from its sensitising potential.
The eMSCA agrees on this evaluation.

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Proper RMM should be envisaged by the Registrant(s) in case the workers are involved in different tasks during the shift in manufacturing and Industrial end-uses.

7.13. Risk characterisation

The RCRs recalculated by the eMSCA using the corrected inhalation DNEL for workers are all below 1.

However, on the basis of the exposure assessment made by the Registrant(s) using the ECETOC Targeted Risk Assessment Model (Integrated version 2010), the inhalation RCR for M2 (Manufacturing-centrifuge/drying/discharge) and the combined one (inhalative and dermal) is corresponding to 1.4 (being the dermal RCR value of 0.0068).

Consequently the CSR should be updated by the Registrant(s) taking into account the DNEL recalculated by eMSCA and additional RMM should be considered.

7.14. References

Burnett C. M., Re T. A., Rodriguez S.,. Loehr R. F and Dressler W. E. (1989). The Toxicity of *p*-aminophenol in the Sprague-Dawley Rat: Effects on Growth, Reproduction and Foetal Development. Food Chem. Toxicol. Vol. 27, No. 10, pp. 691-698.

Unpublished study report (1990). Study to Evaluate the Potential of *p*-aminophenol to induce Unschedule DNA Synthesis in Rat Liver Using an In vivo/in vitro procedure.

Dossou KG, Sicard C, Kalopissis G, Reymond D and Schaefer H. Method for assessment of experimental allergy in guinea pigs adapted to cosmetic ingredients. Contact Dermatitis 13:226–234 (1985).

Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health Version: 2.1 November 2012.

Kleniewska, D. and Maibach, H. Allergenicity of Aminobenzene Compounds: Structure/Function Relationships. Dermatosen 28, 11 – 13 (1980).

Majeska, J. B. et al. Genotoxic Effects of *p*-Aminophenol in Chinese Hamster Ovary and Mouse Lymphoma Cells: Results of a Multiple Endpoint Test. Environmental and Molecular Mutagenesis 23, 163-170 (1995)

Unpublished study report (1990). Study to Evaluate the Chromosome Damaging Potential of *p*-aminophenol by its effecs on cultured human lymphocytes using an in vitro cytogenetic assay.

Unpublished study report (1998b). Reverse Mutation Test of 4-Aminophenol on Bacteria.

Unpublished study report (1998c). In Vitro Chromosomal Aberration Test of 4-Aminophenol on Cultured Chinese Hamster Cells.

Unpublished study report, (1995). Micronucleus Test by Oral Route (Gavage) in Rats for 13 Weeks.

Oberly, T. J. et al. An Evaluation of the CHO/HGPRT Mutation Assay Involving Suspension Cultures and Soft Agar Cloning: Results for 33 Chemicals. Environmental and Molecular Mutagenesis 16, 260-271 (1990)

Registration dossier for 4-aminophenol: European Chemicals Agency http://echa.europa.eu/

SCCS (Scientific Committee on Consumer Safety), Opinion on *p*-aminophenol, 13-14 December 2011.

Unpublished study report,(1998). Bacterial Test.

Unpublished, study report 2000. Chromosome Aberration Assay in Bone Marrow Cells of the Rat.

Zeiger, E. (1988). Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ. Mol. Mutagen.,11, Suppl. 12,1-158.

7.15. Abbreviations

AF Assessment factor
BW Body weight
CAS Chemical abstracts service
C&L Classification and labelling
CLP Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR Carcinogenicity, mutagenicity and toxicity to reproduction
CSR Chemical Safety Report
DMEL Derived Minimal Effect Level
DNEL Derived no effect level
eMSCA Evaluating Member State Competent Authority
NOAEC No Observed Adverse Effect Concentration
NOAEL No Observed Adverse Effect Level
LOAEL Lowest-Observed-Adverse-Effect Level
OECD Organisation for Economic Co-operation and Development
RCR Risk characterization ratio
RMM Risk Management Measures
SCCS Scientific Committee on Consumer Safety